SUPPORT FOR THE AMENDMENTS

Claims 2-11, 18, 21, 37, 38, 43, 47, 54-74, and 79-90 were previously canceled.

Claims 1, 12-17, 19, 20, 22-35, 48-53, and 75-78 are canceled herein.

Claims 39 and 44 are amended.

Claims 91-94 are added.

Support for the amendment of Claims 39 and 44 and the introduction of new Claims 91-94 is provided by, at least, original Claims 1 and 21-23, as well as page 9, lines 2-4 and page 11, lines 16-22 of the specification. This amendment corrects an error in claim dependency.

No new matter has been added by the present amendment.

REMARKS

Claims 36, 39-42, and 44-46 are pending in the present application.

The rejection of Claims 1, 12-17, 19-36, 38-46, 48-53, and 75-78 under 35 U.S.C. §103(a) over Uchiyama et al (US 2002/0119164) in view of Kropf et al (US 6,858,214) and Desai (Pharmaceutical Research, vol. 13 (12), 1996, 1838-1845) is obviated in part by amendment and traversed in part.

Applicants make no further statement with respect to the propriety of this ground of rejection as it applies to Claims 1, 12-17, 19, 20, 22-35, 48-53, and 75-78. Solely to expedite examination of Claims 36, 39-42, and 44-46, Applicants have canceled Claims 1, 12-17, 19, 20, 22-35, 48-53, and 75-78 herein.

Thus, the claimed invention is drawn to:

> A process for producing superfine particles comprising superfine pulverizing a β-glucan derived from a water extract of a mushroom, wherein the superfine particles have an average particle diameter of 10 μm or less, as determined in the form of a dispersion in water, wherein said superfine pulverizing includes preparing particles having an average particle diameter of 10 μm or less by mixing a dispersant with an aqueous solution containing said β-glucan derived from said water extract of a mushroom. (See Claim 36).

And,

> A process for producing a composition containing superfine particles comprising superfine pulverizing a β-glucan derived from a water extract of a mushroom, wherein the superfine particles have an average particle diameter of 10 μm or less, as determined in the form of a dispersion in water, wherein said superfine pulverizing includes preparing particles having an average particle diameter of 10 μm or less by mixing a dispersant with an aqueous solution containing a β-glucan derived from a water extract of a mushroom. (See Claim 42).

In the Office Action, the Examiner has maintained the obviousness rejection over the combined disclosures of Uchiyama et al and Kropf et al and Desai. The Examiner's case remains unchanged and apparently the Examiner believes that no amount of evidence and/or expert testimony is persuasive. Specifically, Examiner Brooks feels that the disclosure of β-glucans regardless of source and/or linkage would provide motivation to the artisan to use, modify, or manipulate the same in a way disclosed by any other reference related to β-glucans regardless of source and/or linkage. In other words, Examiner Brooks remains unpersuaded by Applicants demonstration and testimony that the skilled artisan would not find it obvious to modify a disclosure of β-glucans from mushrooms based on a disclosure of β-glucans from yeast.

The Examiner's position as set forth on pages 7-15 of the Office Action is that (a) she believes the *prima facie* rejection is proper, (b) she does not believe that the evidence provided supports a conclusion of unexpected results, (c) the Okumura Declaration irrelevant in view of her position with respect to Suga (2005) at pages 13-14, and (d) any evidence that may suggest an unexpected result is not commensurate in scope with the claimed invention. Applicants disagree with the Examiner on each of these points.

Specifically, Applicants continue to disagree that the Examiner has properly established a *prima facie* case of obviousness, at least, for the reasons of record in the previously filed response. Applicants further submit that, even if a *prima facie* case of obviousness did exist, the evidence of unexpected results presented in the Declaration under 37 C.F.R. §1.132 executed by Yasuyo Suga filed on September 23, 2009 ("the first Suga Declaration"), as supported the Declaration under 37 C.F.R. §1.132 executed by Yasuyo Suga filed on September 27, 2010 ("the second Suga Declaration"), and the Declaration

under 37 C.F.R. §1.132 executed by Ko Okumura, M.D., Ph.D. filed April 21, 2011 ("the Okumura Declaration") are sufficient to rebut the same.

Notwithstanding the Examiner's continued insistence otherwise, Applicants again submit that Uchiyama et al is overly generic and insufficient to stand for the specific premise that the Examiner asserts. Specifically, Applicants submit that the claimed invention specifically relates to a process for producing superfine particles of a β-glucan that are obtained from a water extract of a mushroom. In contrast, Uchiyama et al does not actually disclose or suggest that the water extract disclosed therein contains any β-glucans. In fact, the paragraph [0034] disclosure by Uchiyama et al only relates to methanol extracts and specifically states that the β-glucans are only obtained in specific fractions obtained from this extract. There is nothing in Uchiyama et al to show that when *Agaricus blazei* are processed in accordance with the extraction method disclosed in paragraphs [0032] - [0033] that the fraction would contain any β-glucans or that the specific fractions containing β-glucans could or would be used for any specific purpose.

The Examiner continues to take the position that the disclosure of a water extract in paragraph [0033] would inherently provide β-glucan containing fractions. The Examiner is reminded that "[t]he fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993); *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981).

Even if the artisan would envision such a fraction and/or β-glucans would inherently be present in an aqueous extract of *Agaricus blazei* processed in accordance with the extraction method disclosed in paragraphs [0032] - [0033] of Uchiyama et al, this would only satisfy the first aspect of the claim. It must also be kept in mind that this specific extract

would have to be formed into particles and those particles would have to be "superfine" (e.g., have an average particle diameter of 10 μm or less) and that these particles are prepared by mixing a dispersant with an aqueous solution containing the β-glucan derived from the water extract of a mushroom. At page 11, lines 10-14, the dispersant is defined as:

> The identity of the dispersant is not particularly limited, and examples of the dispersant include surfactants, polymers, sugars, sugar alcohols, glycerides, acids, bases, salts, etc. Among these, an emulsifier as a typical example of the surfactants is preferable, and lecithin can be used more preferably.

Uchiyama et al is again overly general with respect to the meaning of particulates and, as such, fail to direct the artisan to particles as presently claimed by the method as claimed.

Even if the disclosure at the end of paragraph [0033] of Uchiyama et al is viewed, which disclose that the products (i.e., the aqueous extract) can be "freeze dried or concentrated using water or methanol or acetone solutions" and as such could be interpreted as producing "particles" no reference is made to particle sizes and/or the importance of superfine particles. Further, a method of freeze drying or concentrating using water, methanol, or acetone solutions is not the method as claimed. Indeed, it is not seen where Uchiyama et al provide any disclosure or suggestion of mixing a water extract of a mushroom with a dispersant as claimed.

Moreover, Uchiyama et al fails to disclose or suggest the preparation of particles having an average particle diameter of 10 μm or less. The Examiner recognizes the latter deficiency in the disclosure of Uchiyama et al; however, with respect to the particle size, the Examiner cites Kropf et al. Applicants submit that the citation of Kropf et al is misplaced for the reasons set forth in the response filed on January 29, 2009 and September 27, 2010. Specifically, as previously argued, Kropf et al relates to yeast extracts not mushroom extracts which makes a substantial difference with respect to the nature and identity of the β-glucans.

Desai et al is cited as allegedly showing the effect of particle size on the gastrointestinal uptake of biodegradable microparticles. However, Desai et al has no relationship to the particles of the claimed invention (i.e., superfine particles of a water extract of a mushroom).

Applicants have already provided evidence to show that yeast disclosed by Kropf et al are devoid of β-1,6-glucans and that the only β-glucans derived from yeast are β-1,3-glucans or β-glucans having both 1→3-linked and 1→6-linked glucose residues, which are distinct from the β-1,6-glucans derived from mushrooms.

Support for the foregoing is provided by the following references, which were submitted on June 25, 2008:

1. Documents regarding Lentinula edodes (Shiitake) (Lentinan)

   Sasaki T., Takasuka N., Carbohydr. Res., 47, 99 (1976)

   Sasaki T., Takasuka N., Chihara G., Maeda Y. Y., Gann, 67, 191 (1976)

   Saito H., Ohki T., Sasaki T., Biochem. 16, 908 (1977)

2. Document regarding Schizophyllum commune (Sizofiran)

   Tabata K., Ito W., Kojima T. et al Carbohydr. Res., 89, 121 (1981)

3. Document regarding Selerotium (Seleroglucan)

   Falch B H, Espevik T, Ryan Let al. Carbohydr. Res., 329, 587 (2000)

In addition to the foregoing evidence that establishes that mushrooms comprise β-1,6-glucans the following references were filed with the response on January 29, 2009 to show that yeast disclosed by Kropf et al are devoid of β-1,6-glucans in addition to aforementioned references that show that the only β-glucans derived from yeast are β-1,3-glucans or β-glucans having both 1→3-linked and 1→6-linked glucose residues, which are distinct from the β-1,6-glucans derived from mushrooms:

a. "Zymosan", Wikipedia entry retrieved January 26, 2009 at http://en.wikipedia.org/wiki/Zymosan;

b. "β-glucan", Wikipedia entry retrieved January 27, 2009 at http://en.wikipedia.org/wiki/Beta-glucan;

c. Tada R, et al., Glycoconj. J. 25:851-861, 2008;

d. Oshiman K, et al., Planta Med. 8:610-614, 2002.

References (a) - (c) show that β-glucans derived from yeast are mostly β-glucans having β-1,3-linked main chains (partly, having β-1,6-linked branched chains (residues)). Reference (d) shows that β-glucans derived from mushroom has β-1,6-linked main chains, not β-1,6-linked as a residue.

In addition to the foregoing, in the second Suga Declaration, Yasuyo Suga specifically addresses the allegation that the disclosure of β-glucans regardless of source and/or linkage would provide motivation to the artisan to use, modify, or manipulate the same in a way disclosed by any other reference related to β-glucans regardless of source and/or linkage, stating:

> It is my opinion that the skilled artisan would not modify a disclosure of β-glucans from mushrooms based on a disclosure of β-glucans from yeast. This opinion is based on the fact that there are various types of β-glucans, and there are differences in structure between β-glucans from mushrooms and β-glucans from yeast.

Accordingly, Applicants again submit that the extract disclosed by Kropf et al is inconsistent with and not compatible with the disclosure of Uchiyama et al. As such, it is not a proper allegation that Kropf et al compensates for the deficiencies in the disclosure of Uchiyama et al.

In the Office Action bridging pages 8-9, the Examiner attempts to dismiss the foregoing alleging, in part, that "Application cannot prove hot water extracts of mushrooms are void of β(1→3)glucans the type of β-glucans found in yeast." The problem with this allegation and those surrounding it on pages 8-9 is that the Examiner has it backwards, both in terms of the references and the allocation of the burden. First, the real question is whether the art establishes that mushrooms comprise β-1,6-glucans and that yeast disclosed by Kropf et al are *devoid* of β-1,6-glucans. Applicants submit that the foregoing references unequivocally establish this fact. Specifically, the aforementioned references show that the only β-glucans derived from yeast are β-1,3-glucans or β-glucans having both 1→3-linked and 1→6-linked glucose residues, which are distinct from the β-1,6-glucans derived from mushrooms. This is important as it speaks to (a) the lack of motivation to modify Uchiyama et al based on Kropf et al and (b) the lack of the requisite expectation of success in the combination of these references. Second, it is the Examiner that holds the burden of establishing a *prima facie* case of obviousness, which she has not.

Moreover, even if the artisan were to combined the disclosures of Uchiyama et al, Kropf et al, and Desai, Examiners must still "evaluate any evidence of secondary considerations". Indeed, MPEP 2145 directs Examiners as follows:

> If a *prima facie* case of obviousness is established, the burden shifts to the applicant to come forward with arguments and/or evidence to rebut the *prima facie* case. See, e.g., In re *Dillon,* 919 F.2d 688, 692, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990). Rebuttal evidence and arguments can be presented... **by counsel**, *In re Chu*, 66 F.3d 292, 299, 36 USPQ2d 1089, 1094-95 (Fed. Cir. 1995), **or by way of an affidavit or declaration under 37 CFR 1.132**, e.g., *Soni*, 54 F.3d at 750, 34 USPQ2d at 1687; *In re Piasecki*, 745 F.2d 1468, 1474, 223 USPQ 785, 789-90 (Fed. Cir. 1984). However, arguments of counsel cannot take the place of factually supported objective evidence. See, e.g., *In re Huang*, 100 F.3d 135, 139-40, 40 USPQ2d 1685, 1689 (Fed. Cir. 1996); *In re De Blauwe*, 736 F.2d 699, 705, 222 USPQ 191, 196 (Fed. Cir. 1984).

* * *

> Rebuttal evidence may also include evidence that the claimed invention yields unexpectedly improved properties or properties not present in the prior art. Rebuttal evidence may consist of a showing that the claimed compound possesses unexpected properties. *Dillon*, 919 F.2d at 692-93, 16 USPQ2d at 1901... It may also include evidence of the state of the art, the level of skill in the art, and the beliefs of those skilled in the art. See, e.g., *In re Oelrich,* 579 F.2d 86, 91-92, 198 USPQ 210, 214 (CCPA 1978) (Expert opinions regarding the level of skill in the art were probative of the Nonobviousness of the claimed invention.);

It should also be noted that "Evidence of unobvious or unexpected advantageous properties, such as superiority in a property the claimed compound shares with the prior art, can rebut *prima facie* obviousness. "Evidence that a compound is unexpectedly superior in one of a spectrum of common properties . . . can be enough to rebut a *prima facie* case of obviousness." No set number of examples of superiority is required. *In re Chupp*, 816 F.2d 643, 646, 2 USPQ2d 1437, 1439 (Fed. Cir. 1987)"

To this end, Applicants again point to the first Suga Declaration in which Applicants showed that when the β-glucan derived from the water extract of a mushroom, which forms aggregates in an aqueous solution, is converted into the superfine particles having an average particle diameter of 10 μm or less (especially, by mixing with a dispersant) (see present claim 14, and page 27, line 19 to page 28, line 21), the resulting product significantly improved incorporation through mucosa so that immune functions can be activated or regulated. Such a result is not obtained when looking at the untreated β-glucan sample. In consideration of the evidence provided in the first Suga Declaration, the Declarant further stated:

> Unexpected results:
> (1) The stabilized fine particle can be prepared from the aggregate by treating β-glucan with lecithin under high temperature and high pressure.

(2) The exertion of an inhibitory effect on tumor growth is dependent on a particle diameter. The critical point is 10 μm, and such effect is produced in case of a particle diameter of 10 μm or less.

(3) β-glucan converted into superfine particle is absorbed in small intestinal Peyer's patch, whereas β-glucan, which is not converted into superfine particle, is not absorbed in small intestinal Peyer's patch.

(4) β-glucan converted into superfine particle is absorbed in small intestinal Peyer's patch to produce an inhibitory effect on tumor growth.

Reasons why these results would be considered unexpected:

(1) For improving absorbability of a substance having a high molecular weight and poor absorbability, such as β-glucan, a method for converting into low molecular weight substance is generally selected.

It is a novel idea that absorbability is poor due to large particle diameter in solution, and thereby such effect is not produced.

There are no reports of a method for enhancing absorbability through a step of converting into superfine particle (instead of a step of converting into low molecular weight substance) to produce such effect, so far.

(2) There are no reports of β-glucan, wherein intestinal absorbability is enhanced to produce such effect, so far.

With respect to Unexpected Results, (1) above, Applicants note that this conclusion directly relates to the claimed invention in that it is unexpected that the stabilized fine particle can be prepared from the aggregate by treating β-glucan with lecithin as a dispersant and under high temperature and high pressure. Thus, the first Suga Declaration clearly illustrates the criticality of the claimed particle size and in so doing rebut even a *prima facie* case of obviousness.

Despite the foregoing, the Examiner alleges that the Desai et al provide a reasonable expectation of the results illustrated in the Declaration for the increased absorption of the superfine particles in small intestinal Peyer's patch to produce an inhibitory effect on tumor growth. The Examiner's basis is that Desai et al shows that absorption into Peyer's patch is directly related to the particle size to be delivered.

Applicants disagree with this allegation and the application of the same to the claims at issue in the present application. To this end, Applicants previously presented the second Suga Declaration which stated:

> With respect to the particle size of β-glucans "wherein the superfine particles have an average particle diameter of 10 μm or less" there is no direct relation between absorbability and the medical effect as supported by the following references are attached to this Declaration:
>
> a. Suga et al., Biotherapy. 17(3):267-273, 2003;
> b. Suga et al., Biotherapy. 19(3):273-278, 2005;
> c. Shen et al., Biomedial Research. 28(2):71-77, 2007.
>
> Moreover, when finding the ingredient of an orally effective pharmaceutical, for example, even if absorbability is improved to some extent, degradation is apt to occur when the absorbability is enhanced. Even if the degradation does not occur, pharmacological effect is not necessarily produced, and many difficult problems may newly arise. Therefore, even if the particle size becomes smaller, both of absorbability and immune activating effect are not necessarily improved. Thus, the effect of the present invention as demonstrated in the my Declaration under 37 C.F.R. §1.132 executed on September 7, 2009, is unexpected.

Thus, the first Suga Declaration, when viewed together with the second Suga Declaration, clearly illustrates the criticality of the claimed particle size and the unexpected nature of the same.

Despite the foregoing, the Examiner concludes on page 9 of the Office Action mailed November 29, 2010, that "Applicant's evidence of unexpectedness is not persuasive" for the same general reasons that are fully and completely addressed by the foregoing. Aside from the Examiner's failure to sufficiently explain why her opinion trumps the Declaration evidence of record, Applicants submit that the conclusions drawn are not accurate. To further demonstrate the unexpected nature of the results obtained by the claimed invention, Applicants filed on April 21, 2011, the Okumura Declaration. In the Okumura Declaration, Dr. Okumura explains that there is no direct relation between absorbability and the medical

effect (see paragraph 10). As such, Dr. Okumura states that the present invention as demonstrated in the first Suga Declaration, are unexpected.

To support his opinion, Dr. Okumura explains the relevance of Suga et al., Biotherapy. 19(3):273-278, 2005, which discloses a comparison of the anti-tumor effects between three different particle size samples (solutions). It is stated in paragraph 10 of the Okumura Declaration:

> (a) L-LNT: the solution obtained by subjecting Lentinan solution to centrifugation (8,000G, 10 min), and then suspending the precipitation in distilled water again (in which the mean particle size of the solution is approximately 130 μm);
>
> (b) S-LNT: the supernatant obtained through centrifugation (8,000G, 10 min) (in which the mean particle size is below the possible range of measurement (i.e., not more than 0.01 μm); and
>
> (c) M-LNT: the solution obtained by subjecting Lentinan solution to high-pressure homogenized treatment after mixing the solution with a Lecitin solution (in which the mean particle size of the solution is approximately 0.1 μm). (See Figure 1)
>
> As shown in Figure 4, in case of the intraperitoneal administration, three different particle size samples show the same level of anti-tumor effects.
>
> However, in case of oral administration, only M-LNT shows significant anti-tumor effects. Therefore, in case of oral administration, anti-tumor effects are not shown when the particle size becomes too small. Thus, in case of the oral administration, even if the particle size is decreased, the effects are not necessarily improved, and a correlation between the particle size and the effects can not be predicted and would not have been expected.

Accordingly, in view of the first Suga Declaration and the second Suga Declaration, as further supported by the Okumura Declaration, Applicants submit that the evidence of record is sufficient to rebut even a *prima facie* case of obviousness.

Applicants maintain that the evidence of record establishes an unexpected result for the claimed invention. Specifically, the evidence of records shows that the improved incorporation (absorbability) through mucusa and the improved immune activating effect in oral administration are unexpected. In an apparent attempt to avoid drawing the proper

conclusion from this evidence, at page 11, lines 13-14 the Examiner asserts "figures 1, 3, 5 are not visible and figures 2, 4, 6 are not in color". Applicants regret that the Office's electronic filing system is woefully inadequate and is incapable of capturing color images or even any reasonable representation of the electronic files that are submitted.

Accordingly, to assist the Examiner in overcoming this apparent stumbling block, Applicants are hand-filing a new Declaration under 35 U.S.C. §1.132 executed by Yasuyo Suga ("the third Suga Declaration) in which color copies of Figures 1-6 from the first Suga Declaration (i.e., the Declaration under 37 C.F.R. §1.132 executed by Yasuyo Suga filed on September 23, 2009) as attached. The third Suga Declaration attests that the figures contained therein are the same as those appearing in the first Suga Declaration. If the Examiner is still unable to see the color representations in the third Suga Declaration, she is invited to contact the undersigned by telephone and the undersigned will hand deliver a color copy of the third Suga Declaration directly to the Examiner.

With respect to newly added Claims 91-94, Applicants note that these claims further define the process of Claims 36 and 41 as follows:

> wherein the superfine particles are prepared by fine pulverizing treatment comprising mixing a high-pressure emulsifier with an aqueous solution containing said β-glucan derived from said water extract of a mushroom and subjecting the composition after mixing to an emulsifying pressure of at least 800 kgf/cm^2. (see Claims 91 and 93)

At no point do any of Uchiyama et al, Kropf et al, and Desai disclose or suggest fine pulverizing treatment at an emulsifying pressure of at least 800 kgf/cm^2, especially when using lecithin as an emulsifier (see Claims 92 and 94). In view of the failure of these references to disclose a fine pulverizing treatment at an emulsifying pressure of at least 800 kgf/cm^2 and/or when using lecithin as an emulsifier, Applicants submit that a prima facie case of obviousness for this limitation is not found.

In view of the foregoing, withdrawal of this ground of rejection is requested.

Applicants submit that the present application is in condition for allowance. Early notification to this effect is respectfully requested.

Respectfully submitted,

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